(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2007 (26.04.2007)

PCT

(10) International Publication Number
WO 2007/045009 A1

(51) International Patent Classification:
A61K 31/785 (2006.01) *A61F 6/10* (2006.01)
A61F 6/04 (2006.01) *A61P 31/12* (2006.01)
A61F 6/08 (2006.01) *A61P 31/18* (2006.01)

(21) International Application Number:
PCT/AU2006/000120

(22) International Filing Date: 1 February 2006 (01.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2005905750 18 October 2005 (18.10.2005) AU

(71) Applicant *(for all designated States except US)*: **STARPHARMA PTY LIMITED** [AU/AU]; Baker Building, 75 Commercial Road, Melbourne, Victoria 3004 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GROGAN, Owen, Timothy** [AU/AU]; 3/36 Middleton Street, Black Rock, Victoria 3193 (AU). **MCCARTHY, Thomas, David** [AU/AU]; 40 Tooronga Road, Malvern East, Victoria 3145 (AU).

(74) Agent: **FREEHILLS PATENT & TRADE MARK ATTORNEYS**; Level 43, 101 Collins Street, Melbourne, Victoria 3000 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

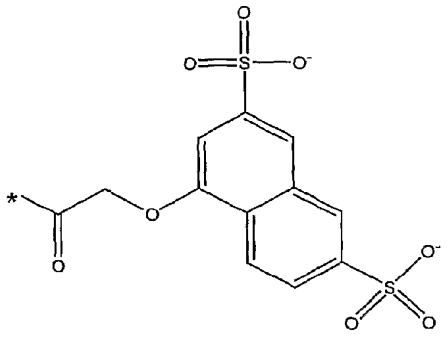
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MICROBICIDAL DENDRIMER COMPOSITION DELIVERY SYSTEM



(IV)

(57) Abstract: A microbicidal delivery system including: a microbicidal composition including a microbicidal compound including a dendrimer including one or more surface groups of formula (IV); a microbicidally active derivative thereof, or pharmaceutically acceptable salt or solvate thereof; and a carrier, excipient or diluent therefor; and a prophylactic device; the microbicidal composition being carried on a surface of the prophylactic device and being compatible therewith.

WO 2007/045009 A1

Microbicidal dendrimer composition delivery system

The present invention relates to the prevention and treatment of sexually transmitted infections and, in particular, relates to the use of a condom carrying a dendrimer having naphthyl disulfonate terminal groups.

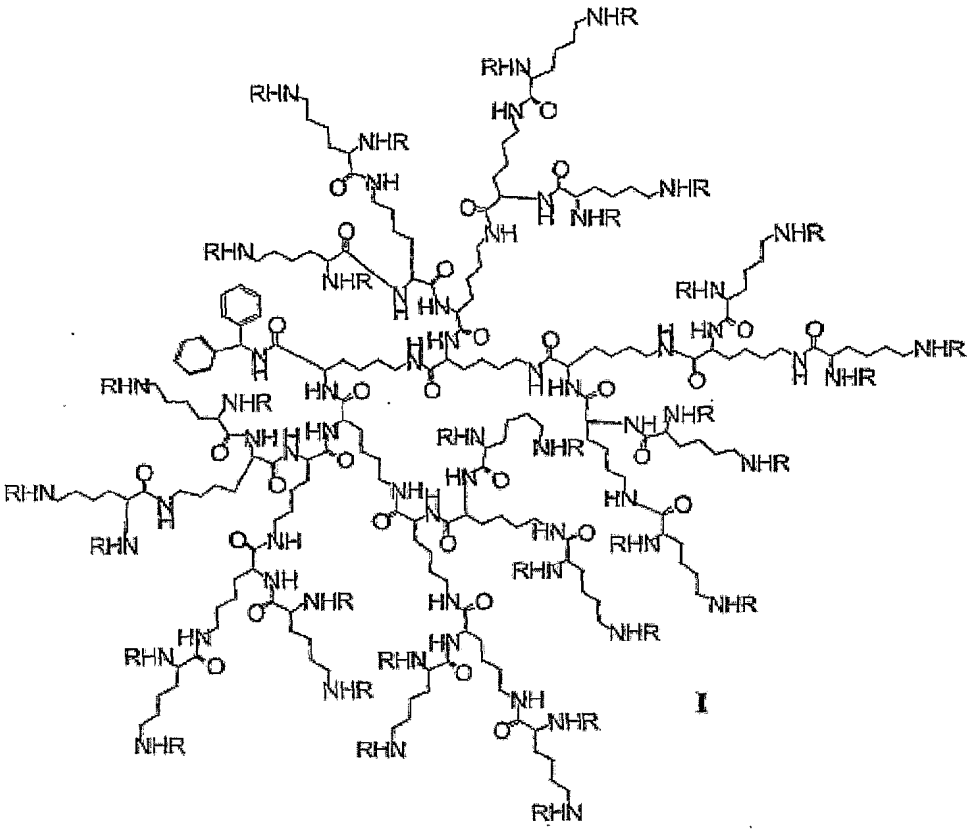
The global incidence of morbidity and mortality of sexually transmitted infections (STIs) caused by Human Immunodeficiency virus (HIV), Herpes virus (HSV) and other viral and microbial pathogens is estimated at several hundred million individuals worldwide. One approach to control the transmission of STIs is the use of topically applied, female/male controlled vaginal or rectal microbicides that inactivate the relevant pathogens.

It has further been found that the use of detergent-based microbicides such as nonoxynol-9 (N-9) may have adverse effects in the prevention of HSV-2 or HIV. Whilst such detergents act by disrupting HSV and HIV membranes, they may also compromise the natural vaginal barrier and significantly increase susceptibility to infection.

International patent application no PCT/AU02/00407 (WO 02/079299), to applicants, the contents of which are incorporated herein by reference, discloses a class of dendrimers, (highly branched macromolecules with a definite envelope of polyanionic or cationic surface groups) which have been shown to exhibit a range of antiviral and antimicrobial activity with minimal toxicity.

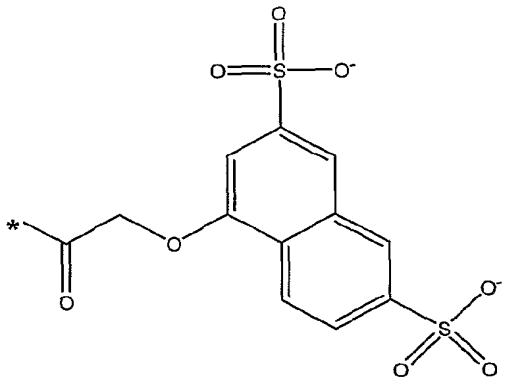
In antiviral and antimicrobial testing, a subset of these dendrimer structures have unexpectedly shown exceptional activity against a broad spectrum of microorganisms associated with sexually transmitted infection that makes them agents of choice for the development of a vaginal or rectal microbicide for the treatment or prophylaxis of sexually transmitted infections.

One compound in particular, SPL7013, formula I,



I

where R represents a group of the formula IV



IV

or a pharmaceutically acceptable salt or solvate thereof; for example,

has been found to have activity against various sexually transmitted infections.

SPL7013 consists of a polylysine dendrimer scaffold with the active surface groups consisting of 32 naphthyl disulphonic acid groups. Each of the naphthyl disulphonate surface groups is attached to the branched dendrimer scaffold with an amido-methyleneoxy linkage to the 32 terminal groups.

There are a number of options for the administration of the type of compound represented, for example, by formula I or a pharmaceutically acceptable salt or solvate thereof, in the treatment or prophylaxis of sexually transmitted infections, for example topical administration. A variety of topical administration routes are available. The particular mode selected will depend, of course, upon the particular condition being treated and the dosage required for preventative efficacy. Such modes of administration include the vaginal, rectal, oral and trans-dermal routes. Suitable formulations for topical, particularly vaginal or rectal, administration include solutions, suspensions, gels, lotions, foams, films, jellies, and creams as well as discrete units such as suppositories and microencapsulated suspensions. Other delivery systems can include sustained release delivery systems which can provide for slow release of the active component of the invention, including sustained release gels, creams, suppositories, or capsules.

However, some of the topical modes of administration may have some disadvantages. For example, vaginal or rectal suppositories may not provide medication to the entire vagina or rectum due to their shape and/or placement in the vagina or rectum by the user. In addition, the medication being supplied by the suppositories may drain out of the vagina or rectum rather quickly, thus reducing the potential effectiveness of the medication. Similarly, the application of topical formulations in the form of a foam, jelly, cream or film may be messy, and the effectiveness of the formulation may be reduced due to drainage of the formulation from the vagina or rectum.

Barrier methods, for example, condoms, are also used to prevent sexually transmitted infections. However, condoms have been known to rupture due to stresses, caused by, for example, stretching or incorrect use. Condoms may also develop microscopic leaks, or may contain small perforations that may lead to transfer of bodily fluids across the barrier, leading to risk of infection.

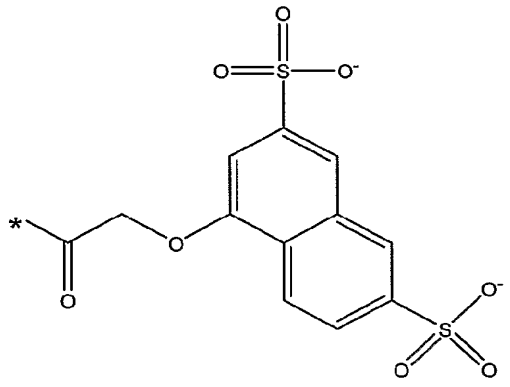
It is, accordingly, an object of the present invention to overcome or at least alleviate one or more of the difficulties and deficiencies related to the prior art.

Summary of the invention

In a first embodiment of the present invention, there is provided a microbicidal delivery system including:

a microbicidal composition including

a microbicidal compound including a dendrimer including one or more surface groups of formula IV



IV,

a microbicidally active derivative thereof, or pharmaceutically acceptable salt or solvate thereof; and

a carrier, excipient or diluent therefor; and

a prophylactic device;

the microbicidal composition being carried on a surface of the prophylactic device and being compatible therewith.

Detailed description of the invention

As used herein in this specification and claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "a macromolecule" includes one or more such macromolecules.

By the term "comprises" (or its grammatical variants) as used herein in this specification and claims is equivalent to the term "includes" and should not be taken as excluding the presence of other elements or features.

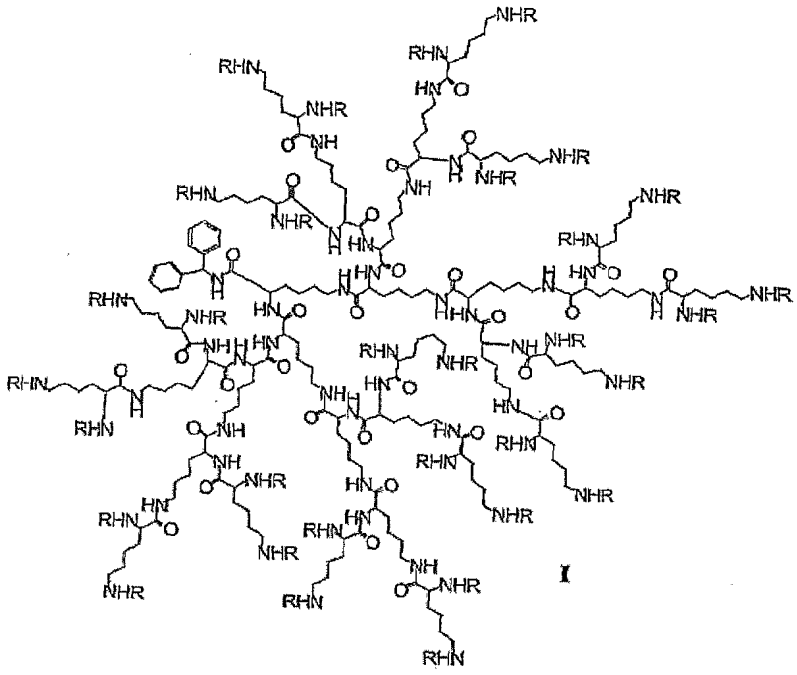
By the term "surface of the prophylactic device" as used herein in the specification and claims, we mean either the internal surface or the external surface or both surfaces of the device.

It has surprisingly been found that the efficacy of the microbicidal composition may be increased by delivery of the composition to the potential site(s) of infection concomitant with sexual activity.

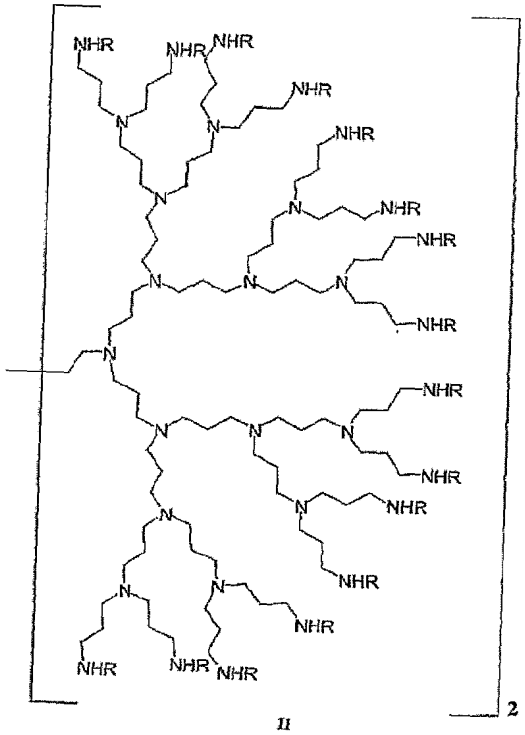
Further, the potential adverse consequences of the partial failure of the prophylactic device may be substantially reduced with the inclusion of the microbicidal composition, as described above.

The delivery system according to this aspect of the present invention may also reduce or eliminate the adverse side effects associated with detergent-based microbicides, resulting in significantly decreased susceptibility to infection with HSV-2 or HIV.

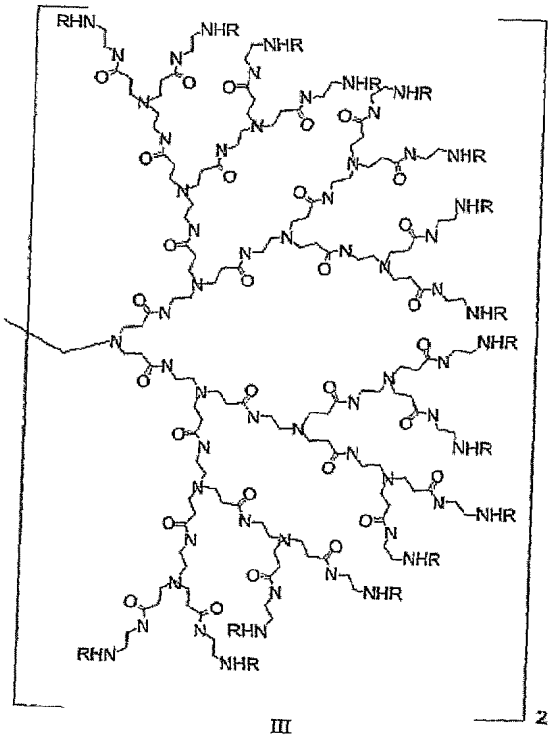
Preferably, the microbicidal compound is selected from one or more of SPL7013 (represented by formula I below), SPL7304 (represented by formula II below), SPL7320 (represented by formula III below), where R in each case is represented by the group of formula IV; a microbicidally active derivative thereof, and a pharmaceutically acceptable salt or solvate thereof.



I

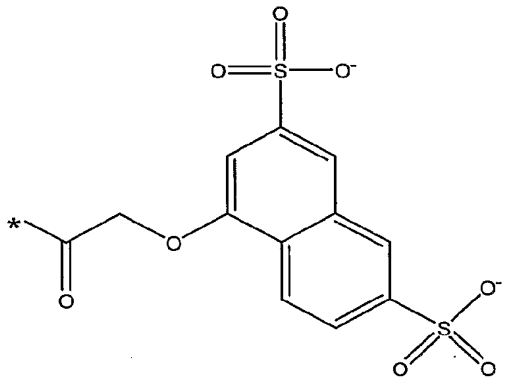


II



III

where R represents a group of the formula IV



IV.

The structures of these compounds consist of a polylysine dendrimer, a polypropyleneimine dendrimer, and a polyamidoamine (PAMAM) dendrimer scaffold respectively, with the active surface groups consisting of 32 naphthyl disulphonic acid groups as sodium salts. Each of the naphthyl-disulphonate functional surface groups is attached to the branched dendrimer scaffold with an amido-methyleneoxy linkage to the 32 terminal groups. The compound SPL7013 is preferred.

As described above, the compounds SPL7013, SPL7304, and SPL7320 are preferred compounds of the present invention, and have been found to exhibit significant antiviral activity, particularly against viral and microbial vectors of the most common sexually transmitted infections. Common sexually transmitted infections include, but are not limited to papillomaviruses, *Chlamydia trachomatis*, *Candida albicans*, *Trichomonas vaginalis*, Herpes simplex viruses, Cyclomegalovirus, *Neisseria gonorrhoeae*, Human Immunodeficiency viruses, *Treponema pallidum*, Hepatitis B and C viruses, *Calymmato bacterium granulomatis*, *Haemophilus ducreyi*, *Sarcoptes scabiei*, *Phthirus pubis*, *Mycoplasma*, *Gardnerella vaginalis*.

SPL7013 exhibits a broad-spectrum antiviral activity with high efficacy and minimal cell or animal toxicity, against vectors of several of the most important vaginally or rectally sexually transmitted infections. High activity has been determined against genital Herpes virus-2 (HSV-2) both in *vitro* cell tests and *in vivo* in an animal (mouse) model test and *in vitro* cell tests against Herpes virus-1 (HSV-1) and Human Immunodeficiency

viruses (HIV-1 and HIV-2). It has also been shown to be active against the causative agent of genital warts, Human Papillomavirus (HPV), and against the bacterial vector of non-specific urethritis, *Chlamydia trachomatis*. In cell tests, SPL7013 has also shown activity against viral strains of Herpes virus-2 that are resistant to currently used modified nucleoside based antiviral agents. In addition SPL7304 and SPL7320 show high activity against HSV-1, HSV-2, HIV-1, and HIV-2. Furthermore SPL7013, SPL7304 and SPL7320 are active in CD4-dependant and CD4-independent HIV transmission assays, and are effective at preventing HIV-1 attachment and fusion. All compounds have been shown not to inhibit the growth of various species of beneficial Lactobacillus. In addition SPL7013, SPL7304, and SPL7320 have been shown to be effective in the prevention of infection of human peripheral blood monocular cells (PBMCs) with either HIV-1 RoJo or SIV 89. 6pd.

The pharmaceutically acceptable salt or solvate may be of any suitable type. Examples of suitable salts include, but are not limited to metallic salts (for example, aluminium, calcium, lithium, magnesium, potassium, sodium and zinc salts), organic salts (for example, N,N^{I}-dibenzylethylenediamine, chloroprocaine, diethanolamine, ethylenediamine, cyclohexylamine, meglumine, (N-methylglucamine) and procaine), quaternary amines (for example, choline), sulphonium salts and phosphonium salts.

The microbicidal composition preferably has a viscosity such that it remains in contact with the prophylactic device for an extended period of time, and does not flow off the prophylactic device on contact.

As stated above, the microbicidal composition of this embodiment of the present invention includes a carrier, excipient or diluent. The microbicidal composition may be provided in the form of a solution, suspension, lotion, film, jelly, foam, gel, cream and the like. The carrier, excipient or diluent may include one or more of any and all conventional solvents, dispersion media, fillers, solid carriers, aqueous solutions, coatings, viscosity modifying agents, antibacterial and anti fungal agents, isotonic, and absorption enhancing or delaying agents, activity enhancing or delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art, and it is described, by way of example, in *Remington's Pharmaceutical*

Sciences, 18th Edition, Mack Publishing Company, Pennsylvania, USA. Except insofar as any conventional carrier and/or diluent is incompatible with the active ingredient, use thereof in the microbicidal compositions of the present invention is contemplated.

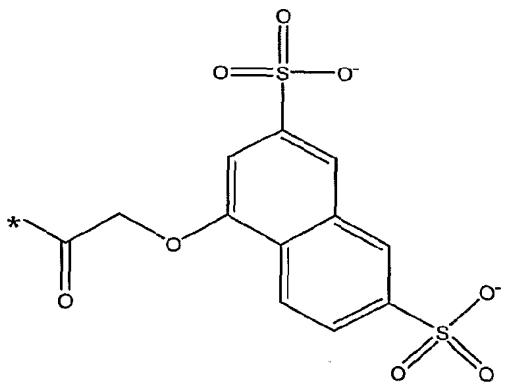
Vehicles suitable for topical administration include oil-in-water and water-in-oil emulsions, white petrolatum, hydrophilic petrolatum, lanolin emulsions, polyethylene glycols, cocoa butter, buffering agents (including Carbopol 971P), emollient oils (e.g. water-soluble oils including, for example, polyethylene glycol), a lubricating gel (including, for example, water, propylene glycol, hydroxyethyl cellulose, benzoic acid and sodium hydroxide), a water-soluble oil (including, for example, glycerine, propylene glycol, polyquaternium #5, methyl paraben and propyl paraben), a cream (including, for example, benzyl alcohol, cetearyl alcohol, cetyl esters, wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate), and the like.

Preferably, the carriers, excipients and/or diluents include one or more of the group consisting of sodium hydroxide, water soluble oils, buffering agents, propylene glycol, glycerine and water. More preferably, the carriers, excipients and/or diluents include sodium hydroxide, edetate disodium dihydrate, methyl paraben, propyl paraben, Carbopol 971P, propylene glycol, glycerine, and purified water in combination.

The microbicidal composition may further include a secondary pharmaceutically active compound.

Accordingly, in a further embodiment of the present invention there is provided a microbicidal composition including

a microbicidal compound including a dendrimer including one or more surface groups of the formula IV



IV

a microbicidally active derivative thereof, or pharmaceutically acceptable salt or solvate thereof;

a secondary pharmaceutically active compound; and

a carrier, excipient or diluent therefor.

The secondary pharmaceutically active component may be exemplified by, but not limited to, one or more of the compounds selected from the group consisting of:

Acetonemia preparations
Anaesthetics
Anti-acid agents
Antibacterials
Anti-convulsivants
Anti-histamines
Anti-inflammatories
Anti-parasitic agents
Anti-STI agent
Antiviral pharmaceuticals
Biologicals
Bronchodilators and expectorants
Cardiovascular pharmaceuticals
Anabolic agents
Analgesics
Anti-arthritic agents
Antibodies
Anti-fungals
Anti-infectives
Anti-microbials
Anti-protozoals
Anti-ulcer agents
Behaviour modification drugs
Blood and blood substitutes
Cancer therapy and related pharmaceuticals
Central nervous system pharmaceuticals

Contrast agents	Contraceptives
Diabetes therapies	Diuretics
Fertility pharmaceuticals	Growth hormones
Growth promoters	Hematinics
Hemostatics	Hormones and analogs
Hormone replacement therapies	Immunostimulants
Minerals	Muscle relaxants
Natural products	Nutraceuticals and nutritionals
Obesity therapeutics	Ophthalmic pharmaceuticals
Osteoporosis drugs	Pain therapeutics
Peptides and polypeptides	Respiratory pharmaceuticals
Sedatives and tranquilizers	Transplantation products
Urinary acidifiers	Vaccines and adjuvants
Vitamins	

Preferably, the secondary pharmaceutically active compound is a contraceptive or an agent active against sexually transmitted infections. More preferably, the secondary pharmaceutically active compound is a contraceptive, most preferably, a spermicide. Examples of contraceptives and agents active against sexually transmitted infections include, but are not limited to, podophyllin, tetracycline, nyastatin, fluconazole, metronidazole, acyclovir, penicillin, cefotaxime, spectinomycin, retrovir, erythromycin, ceftriaxone, cotrimoxazole, benzyl benzoate, malathion, nonoxynol-9, octoxynol-9, menfegol, progestin, estrogen, and estradiol. Other suitable secondary pharmaceutically active components which are contraceptives or agents active against sexually transmitted infections would be known to the person skilled in the art.

The microbicidal composition may be carried on the prophylactic device in any suitable manner. Examples include, but are not limited to, the composition being carried on a surface of the prophylactic device (for example, the internal surface, the external surface or both surfaces of the device), impregnated into the prophylactic device, covalently bound to a surface of the prophylactic device, and the like.

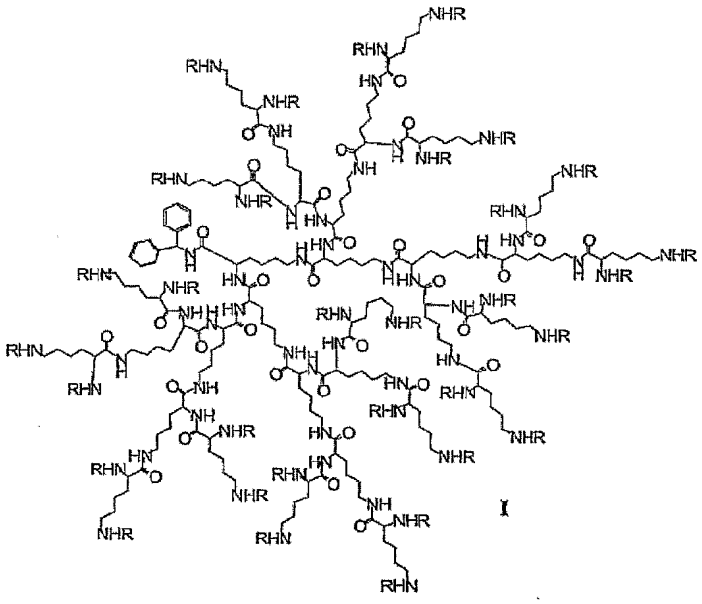
The prophylactic device may be of any suitable type. a condom, a cervical cap, contraceptive diaphragm, vaginal sponge, pessary, or the like may be used. A condom is preferred.

The prophylactic device and microbicidal composition may be selected to ensure compatibility there between.

Where a condom is used as the prophylactic device, the microbicidal composition may be carried on an external surface and/or an internal surface of the condom. Preferably, the microbicidal composition covers at least a substantial portion of the external surface and/or the internal surface of the condom.

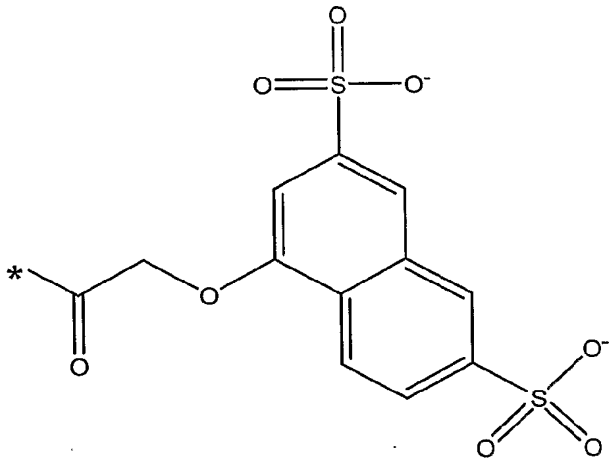
In a preferred aspect of this embodiment of the present invention, there is provided a microbicidal delivery system including

a microbicidal compound of formula I



I

where R represents a group of the formula IV



IV;

a carrier, excipient or diluent therefor; and

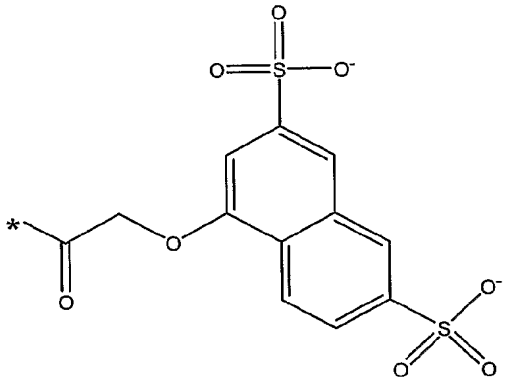
a condom;

the microbicidal composition being carried on a surface of the condom and being compatible therewith.

In a further embodiment of the present invention, there is provided a microbicidal delivery system including

a microbicidal composition including

a microbicidal compound including a dendrimer including one or more surface groups of formula IV



IV

a microbicidally active derivative thereof, or pharmaceutically acceptable salt or solvate thereof;

a secondary pharmaceutically active compound; and

a carrier, excipient or diluent therefor; and

a prophylactic device;

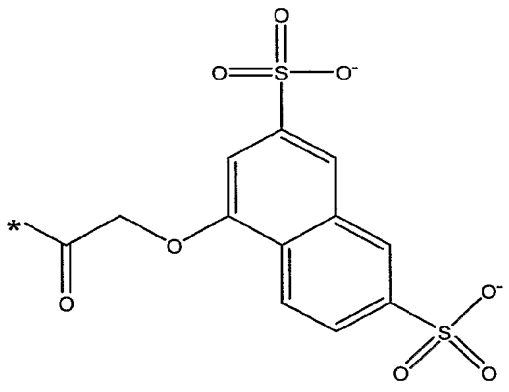
the microbicidal composition being carried on a surface of the prophylactic device and being compatible therewith.

Preferably the secondary pharmaceutically active compound is an agent active against sexually transmitted infections.

In another embodiment of the present invention, there is provided a method for the prevention of sexually transmitted infections in a human patient, including providing a microbicidal delivery system, including:

a microbicidal composition including

a microbicidal compound including a dendrimer including one or more surface groups of formula IV



IV

a microbicidally active derivative thereof, or

a pharmaceutically acceptable salt or solvate thereof; and

a carrier, excipient or diluent therefor; and

a prophylactic device;

the microbicidal composition being carried on a surface of the prophylactic device and being compatible therewith.

The microbicidal compound may be present in any suitable amounts. The amount of microbicidal composition should be sufficient for the reduction or prevention of sexually transmitted infections. This amount may depend on the particular sexually transmitted infection sought to be prevented, and individual patient parameters including age, physical condition, size, weight and concurrent treatment(s). These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

The weight % of microbicidal compound included in the microbicidal composition according to the present invention may be in the range of about 0.5% to 20% weight/weight, more preferably in the range of about 1% to 18% weight/weight, most preferably in the range of about 2% to 15% weight/weight.

The microbicidal composition according to the present invention may be administered in an amount sufficient for the prevention of sexually transmitted infections. This amount may depend on the particular sexually transmitted infection sought to be prevented, and individual patient parameters including age, physical condition, size, weight and concurrent treatment(s). These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

The amount of microbicidal composition included in the microbicidal delivery system according to the present invention may be in the range of 0.25 g to 2 g. When the microbicidal composition is applied to the outside surface of the prophylactic device, the amount of microbicidal composition is preferably between about 0.5 g to 2.0 g, more preferably between about 0.75 g to 1.75 g, most preferably between about 1.0 g to 1.5

g. When the microbicidal composition is applied to the inside of the prophylactic device, the amount of microbicidal composition is preferably between about 0.1 g to 1.0 g, more preferably between about 0.15 g to 1.0 g, most preferably between about 0.25 to 0.65 g.

Further features of the present invention will be apparent from the following Examples which are included by way of illustration, not limitation, of the invention.

Examples

Example 1 - Preparation of microbicidal composition (3% active).

Table 1 - Ingredients for 3% microbicidal composition

Ingredient	Monograph	Quantity per batch (kg)
Excipients		
Sodium Hydroxide NF	NF	0.1443
Edetate Disodium Dihydrate USP	USP	0.010
Methylparaben NF	NF	0.018
Propylparaben NF	NF	0.002
Carbopol 971P NF	NF	0.500
Propylene Glycol USP	USP	0.100
Glycerin USP	USP	0.100
Purified Water I	USP	1.804
Purified Water II	USP	8.370
Active Pharmaceutical Ingredients		
SPL7013		0.339

Protocol

i. The equipment is sanitised and rinsed prior to manufacture.

ii. In a stainless steel jug, Sodium Hydroxide, NF, is dissolved in purified water.

iii. In a stainless steel vessel, Edetate Disodium Dihydrate, USP, is added to purified water and stirred with a high shear mixer until dissolved.

iv. Methyl- and Propyl- paraben, NF, are added one at a time and mixed until fully dispersed.

v. Carbopol 971P, NF, is added slowly and the mixture stirred until the Carbopol 971P, NF, is fully dispersed and a smooth gel is formed.

vi. Propylene glycol, USP, and Glycerin, USP, are added to the vessel and the solution mixed until the contents are fully dispersed.

vii. Sodium Hydroxide solution from Step ii. is added until the pH is 4.5.

viii. Following pH measurement, purified water is added to volume and the solution mixed until all ingredients are dispersed and a homogeneous gel is formed.

ix. The bulk yield is measured.

Example 2 – Condom Stability Study 1%, 3% and 5% of active in Carbopol gel.

Individually packaged male condoms made from natural rubber latex and intended for single use meet with certain minimum requirements specified in ASTM Designation: D 3492-97 (American Society for Testing and Materials, Standard Specification for Rubber Contraceptives, Male Condoms) test method. The test method is designed to ensure that condoms are of consistent quality. Certain ingredients in vaginal formulations may compromise condom integrity. This method was used to determine the effect of vaginal formulations on condoms. The following parameters were determined for the treated and untreated condoms: pressure at burst, volume at burst, length, thickness, and width. If the formulation compromises the condoms, the pressure and volume at burst are expected to be lower. The length of the condoms might be affected as well.

A 4.0 g sample of gel was spread on 7.5 cm x 410 cm aluminium foil and wrapped around a condom. The condom was placed on polypropylene dowel and dowel was wrapped with the aluminium foil containing the test article. After 30 min the aluminium foil was removed and the condom was blotted free of adhering gel. The length, width volume, and pressure at burst of the treated condoms were then measured.

Air Burst Properties (Pressure and Volume at Burst)

1. Carry out the test at 25 ± 5°C.
2. Unroll the condom onto the mount without stretching. The length of condom tested should be 150 ± 3 mm (uninflated).
3. Seal the condom to the system with the inflatable rubber ring (this rubber ring clamps off a constant length of the condom).
4. Ensure that air cannot leak through the seal or from the system during inflation.
5. Open the valve controlling the air to the condom and at the same time initiate the chart recorder.
6. Inflate the condom at a constant rate of 0.4 to 0.5 L/s (24 to 30 L/min). Record the flow rate.
7. Pressure is recorded as a function of time until the condom bursts. An immediate rise in the pressure is observed indicating initial time. At burst the pressure returns to zero.
8. Record the bursting pressure (to nearest 0.1 kiloPascals (kPa)) and calculate the bursting volume (to nearest 0.5 L). The pressure at burst can be read from the recording on the chart paper. The volume at burst is calculated using the following equation:

Volume at burst (L) = Flow rate x time from initiation of study to burst

Data for this experiment is provided in Table 2.

Table 2 – Exposure of condoms to vaginal gels for 30 minutes.

Treatment	Untreated			Treated for 30 Minutes			Result
	Burst pressure (kPa)	Time to Burst (sec)	Burst volume (L)	Burst pressure (kPa)	Time to Burst (sec)	Burst volume (L)	
Placebo	1.97	84	38.27	1.96	80	36.43	Not compromised
1% gel	1.97	84	38.27	1.86	83	37.85	Not compromised
3% gel	1.97	84	38.27	1.82	82	37.58	Not compromised
5% gel	1.97	84	38.27	1.91	87	40.03	Not compromised

Measurement of Length

1. Unroll the condom and smooth out the wrinkles (this is not necessary for treated condoms).
2. Put the condom on the mandrel and let it hang freely, stretched only by its own mass.
3. Note, to the nearest millimetre, the length of the condom as indicated on the scale outside the open end of the condom.

Measurement of Width

1. Unroll the condom and smooth out the wrinkles (this is not necessary for treated condoms).
2. Place the condom on a flat surface.
3. Measure to the nearest 0.5 mm the width of the condom laid flat at a distance of 30 ± 5 mm from the open end.

Data from these assays is provided in Table 3.

Table 3 – Condom dimensions, Burst Strength and Burst Volume after treatment with microbicidal composition

Condom	Treatment	Before Dipping Dimensions (mm)		After dipping Dimensions (mm)			Burst pressure (kPa)	Burst Volume (L)	Average Volume (L)
		Length	Width	Length	Width	Time to Burst (s)			
1	Plain (control)	182	53			85	1.98	38.99	38.27
2	Plain (control)	185	53			83	1.9	37.93	
3	Plain (control)	184	53			83	2.02	37.88	
1	Placebo gel	185	53	187	53	70	1.69	32.22	36.43
2	Placebo gel	184	53	186	53	83	2.10	37.85	
3	Placebo gel	185	53	185	53	86	2.09	39.23	
1	1% composition	185	53	186	53	83	1.9	37.93	37.85
2	1% composition	186	53	185	53	82	1.89	37.65	
3	1% composition	186	53	184	53	83	1.79	37.97	
1	3% composition	186	53	187	53	89	1.95	40.65	37.58
2	3% composition	187	53	189	53	88	1.96	40.38	
3	3% composition	186	53	187	53	69	1.55	31.71	
1	5% composition	185	53	187	53	90	1.72	41.3	40.03
2	5% composition	185	53	185	53	82	1.9	37.65	
3	5% composition	186	53	185	53	80	2.1	41.14	

References

1. ASTM Designation: D 3492-97, Standard Specification for Rubber Contraceptives (Male Condoms).
2. Condom Burst Test on a Placebo and Active Gel Formulation, CDDR-R4316-0600-NL-3, Pages 106 of 108 and 107 of 108, June 26, 2000.

Example 3 – Evaluation of the effect of the microbicidal composition on condoms

This investigation assesses the condom strength (using the Burst Test) of condoms lubricated with the microbicidal composition according to the present invention before and after ageing for 7 days at 70 °C.

The condoms tested were: DF 53 N Thin, Batch no.: 0509052516 and the tests were conducted in S&T, Shah Alam.

Procedure

1. 0.5g of the microbicidal composition containing 3% (w/w) of the active was dosed onto the external and internal surfaces of the condom (total: 1.0 g) and sealed in an aluminium foil (56 mm x 56 mm);

2. 160 pcs of the condoms were prepared, 80 pcs were kept in an oven at 70 °C for 7 days (aged) for an accelerated shelf life study and the balance 80 pcs were tested without ageing (unaged samples).

3. All of the unaged and aged sample were tested for Burst properties.

Results

Burst properties (Tested ISO 4074:2002 Standards)

Batch no.	Burst Unaged						Burst aged (7 days, 70 °C)					
	MV	SDV	NCV	MP	SDP	NCP	MV	SDV	NCV	MP	SDP	NCP
0509052516	51.34	5.93	0	1.63	0.18	2	44.14	3.01	0	1.49	0.10	0

Remarks: MV – Mean volume, SDV – Standard deviation of volume, NCV – Non-compliance of volume, MP – Mean pressure, SDP – Standard deviation of pressure, NCP – Non-compliance of pressure

Results of the Burst Test showed that the microbicidal composition containing 3% (w/w) of the active has caused a significant drop in the mean volumes and pressure by 14.0% and 8.6% respectively but both mean volumes and pressures were well above the accepted criteria (Burst volume: 18 litres, Burst pressure: 1kPa) Therefore, we conclude that even though the microbicidal composition containing 3% (w/w) of the active has significantly reduced the burst volume and pressure of the condom (DF 53 Thin) the effect is still acceptable.

Example 4 – Migration test for the microbicidal composition containing 3% (w/w) of the active

Sample: Bulk condom DF 53N Thin, the microbicidal composition containing 3% (w/w) of the active

Dosing:
1. 0.5 g internal & external condom
2. 0.5 g external only

Results

Condoms were prepared according to Example 3 above, and were kept at room temperature and tested for lubricant migration every week for 7 weeks. The condoms were unrolled carefully and placed on a piece of clean paper. The distance travelled by the lubricant from the teat of the condom was measured by a ruler.

Date	Ageing time/weeks	Samples	Dosing internal & external			Dosing external only		
			1	2	mean	1	2	mean
6-Oct-05	0 (24 hours)	1	2.50	4.00	**3.25**	3.50	2.00	**2.75**
		2	2.80	3.60	**3.20**	2.00	1.90	**1.95**
					3.23			2.35
13-Oct-05	1	1	3.40	4.00	**3.70**	0.90	2.50	**1.70**
		2	2.10	2.00	**2.05**	2.50	1.20	**1.85**
					2.88			1.78
20-Oct-05	2	1	3.90	2.00	**2.95**	2.70	2.70	**2.70**
		2	1.70	4.00	**2.05**	2.80	2.80	**2.55**
					2.50			2.63
27-Oct-05	3	1	2.40	3.50	**2.45**	2.70	2.20	**2.45**
		2	2.70	3.20	**2.95**	2.50	2.50	**2.50**
					2.70			2.48
3-Nov-05	4	1	-	-	-	-	-	-
		2	-	-	-	-	-	-
10-Nov-05	5	1	3.90	3.30	**3.60**	2.30	2.10	**2.20**
		2	3.20	2.90	**3.05**	2.60	3.10	**2.85**
					3.33			2.53
17-Nov-05	6	1	3.10	3.30	**3.20**	3.20	2.70	**2.95**
		2	2.00	2.50	**2.25**	1.90	2.40	**2.15**
					2.73			2.55
24-Nov-05	7	1	2.80	4.80	**3.80**	2.90	3.00	**2.95**
		2	3.90	2.80	**3.35**	1.50	1.70	**1.60**
					3.58			2.28

Example 5 – Study to Assess the Effect of the microbicidal composition according to the present invention on HSV-2 Susceptibility

Background

The study was conducted to detect potential adverse effects of the microbicidal composition according to the present invention by measuring susceptibility of mice to infection with herpes simplex virus type 2 (HSV-2), the virus that most commonly causes genital herpes.

The mouse HSV-2 vaginal transmission model is used by Richard Cone at Johns Hopkins University, Baltimore, USA, to assess toxicities associated with microbicides that could lead to susceptibility to pathogens such as HSV-2.

Methods

Mouse Model:

Prior to the susceptibility assessment, female CF-1 mice (Harlan, Indianapolis, IN, USA) 6-8 weeks old are progestin treated (Depo Provera®, medroxyprogesterone acetate) to increase HSV-2 susceptibility, and to make the mice more uniform in terms of susceptibility than mice at different stages of the oestrous cycle.

Viral Inoculum:

Strain G of HSV-2, $5x10^8$ $TCID_{50}$/mL.

Procedures:

20 µL of the microbicidal composition according to the present invention was administered to the vagina followed 12 hours later by administration of a low-dose inoculum of HSV-2 (0.1 ID_{50}) delivered in 10 µL of Bartels medium. Control animals received 20 µL of PBS instead of test product.

The inoculum is delivered 12 hours after application of the test product because previous experiments showed that this was the time at which peak susceptibility to HSV-2 infection occurred following administration of nonoxynol-9.

In this study, a total of 40 mice received the microbicidal composition according to the present invention and a total of 40 mice received PBS.

Results

Only 1 out of the 40 mice treated with the microbicidal composition according to the present invention became infected with HSV-2. In contrast, 7 out of 40 mice in the control group became infected. In other words, there was no increase in susceptibility following administration of the microbicidal composition according to the present invention.

In previous studies, 29 out of 42 animals treated with nonoxynol-9, 20 out of 30 animals treated with microbicide ingredient 1, and 25 out of 41 animals treated with microbicide ingredient 2, became infected.

To determine relative susceptibility of the mice in previous studies, two groups of control mice were treated with PBS for every group of mice treated with test product. One control group was inoculated with 0.1 ID_{50}, while the other was inoculated with 10 ID_{50}. The fraction of animals infected in each control group was then used to construct a dose-response graph (fraction infected vs. log ID), drawing a linear interpolation between the low and high dose points. The fraction of mice infected in the test group was then plotted on this graph to determine the effective ID of the low-dose inoculum in this test group. Relative susceptibility was defined as the effective ID the low-dose inoculum delivered to the test mice divided by the ID it delivered to the control animals.

Animals treated with nonoxynol-9 were 29.7 times more susceptible to HSV-2 infection than the control animals ($P<0.001$, Fishers exact two-sided t-test), while animals treated with microbicide ingredients 1 and 2 were 29.1 ($P<0.001$) and 17.5 ($P<0.001$) times more susceptible, respectively.

Conclusion

The microbicidal composition according to the present invention does not appear to lead to increased susceptibility in the mouse-model of HSV-2 infection. Nonoxynol-9 and other detergent microbicides may lead to increased susceptibility.

Reference

Cone RA, Hoen TE, Wang XX & Moench TR. Microbicidal Detergents Increase HSV Susceptibility in Mice Without Causing Visible Epithelial Defects. Abstract # 02421, "Microbicides 2004" Conference, London, UK; March 2004.

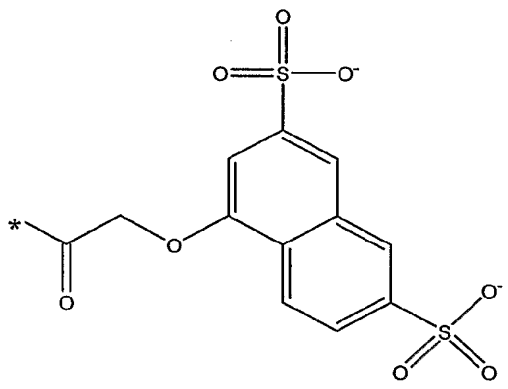
It will be appreciated that variations and modifications may be made to the invention as broadly described herein, other than those specifically described without departing from the spirit and scope of the invention. It is to be understood that this invention extends to include all such variations and modifications.

The claims defining the invention are as follows:

1. A microbicidal delivery system including:

a microbicidal composition including

a microbicidal compound including a dendrimer including one or more surface groups of formula IV



IV

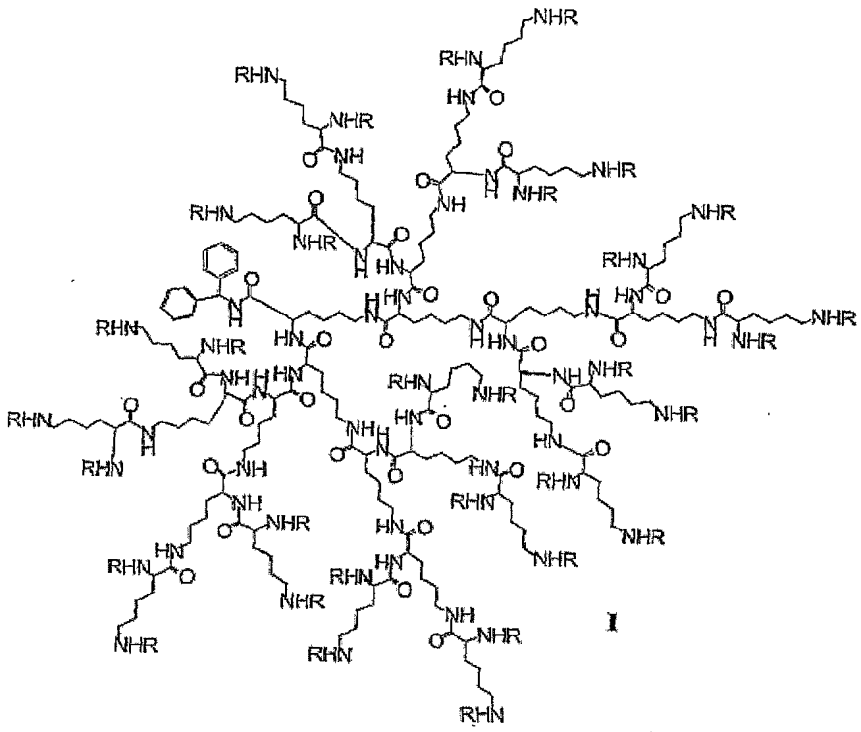
a microbicidally active derivative thereof, or pharmaceutically acceptable salt or solvate thereof; and

a carrier, excipient or diluent therefor; and

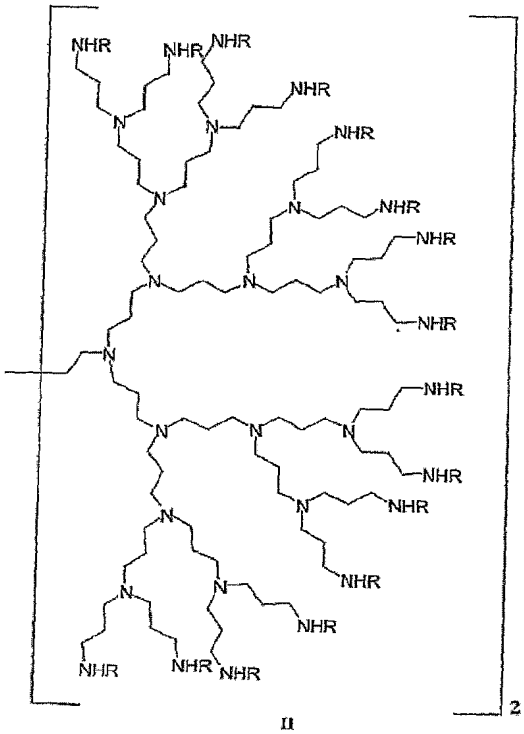
a prophylactic device;

the microbicidal composition being carried on a surface of the prophylactic device and being compatible therewith.

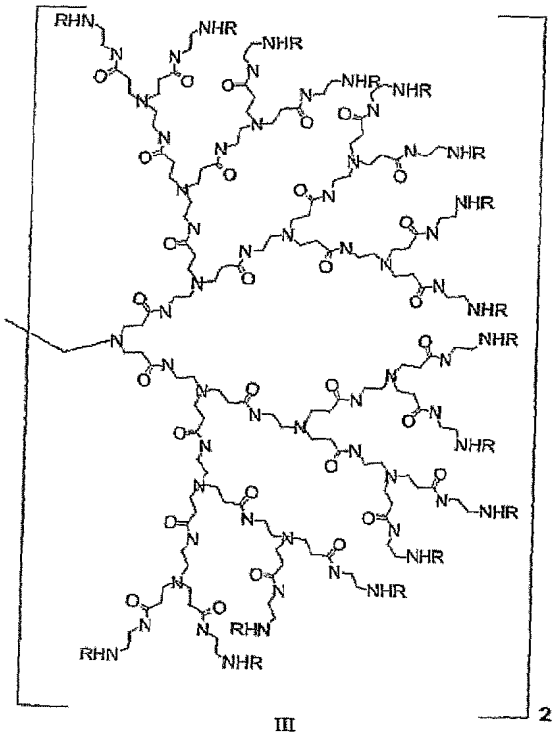
2. A microbicidal delivery system according to claim 1 wherein the microbicidal compound is selected from one or more of the compounds of formula I, II or III



I

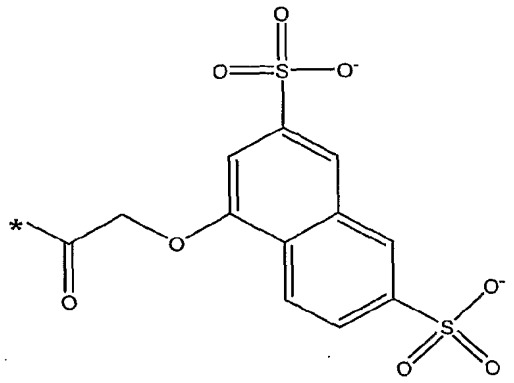


II



III

where R represents a group of the formula IV



IV.

3. A microbicidal delivery system according to claim 2 wherein the microbicidal compound is the compound of formula I.

4. A microbicidal delivery system according to claim 2, wherein the microbicidal compound is a pharmaceutically acceptable salt of the compound of formula I, II or III.

5. A microbicidal delivery system according to claim 4, wherein the salt is a metallic salt selected from the group consisting of one or more of aluminium, calcium, lithium, magnesium, potassium, sodium and zinc salts.

6. A microbicidal delivery system according to claim 4, wherein the salt is an organic salt selected from the group consisting of one or more of N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, ethylenediamine, cyclohexylamine, meglumine (N-methylglucamine) and procaine.

7. A microbicidal delivery system according to claim 4, wherein the salt is selected from one or more of the group consisting of one or more of a quaternary amine, a sulphonium salt and a phosphonium salt.

8. A microbicidal delivery system according to claim 1, wherein the carrier, excipient or diluent includes one or more of the group consisting of sodium hydroxide, water soluble oils, buffering agents, propylene glycol, glycerine and water.

9. A microbicidal delivery system according to claim 1 wherein the microbicidal compound is present in the microbicidal composition in an amount of from about 0.5% to 20% weight/weight.

10. A microbicidal delivery system according to claim 9 wherein the microbicidal compound is present in the microbicidal composition in an amount of from about 2% to 15% weight/weight.

11. A microbicidal delivery system according to claim 1 wherein the microbicidal composition is present in an amount of from about 0.25 to 2 g.

12. A microbicidal delivery system according to claim 1, wherein the microbicidal composition further includes a secondary pharmaceutically active compound which is a contraceptive or an agent active against sexually transmitted infections.

13. A microbicidal delivery system according to claim 12, wherein the secondary pharmaceutically active compound is a contraceptive.

14. A microbicidal delivery system according to claim 13, wherein the secondary pharmaceutically active compound is a spermicide.

15. A microbicidal delivery system according to claim 12, wherein the secondary pharmaceutically active compound is selected from one or more of the group consisting of podophyllin, tetracycline, nystatin, fluconazole, metronidazole, acyclovir, penicillin, cefotaxime, specinomycin, retrovir, erythromycin, ceftriaxone, cotrimoxazole, cotrimoxazole, benzyl benzoate, malathion, nonoxynol-9, octoxynol-9, menfegol, progestin, estrogen and estradiol.

16. A microbicidal delivery system according to claim 1 wherein the prophylactic device is selected from the group consisting of a condom, cervical cap, contraceptive diaphragm, vaginal sponge or pessary.

17. A microbicidal delivery system according to claim 16 wherein the prophylactic device is a condom.

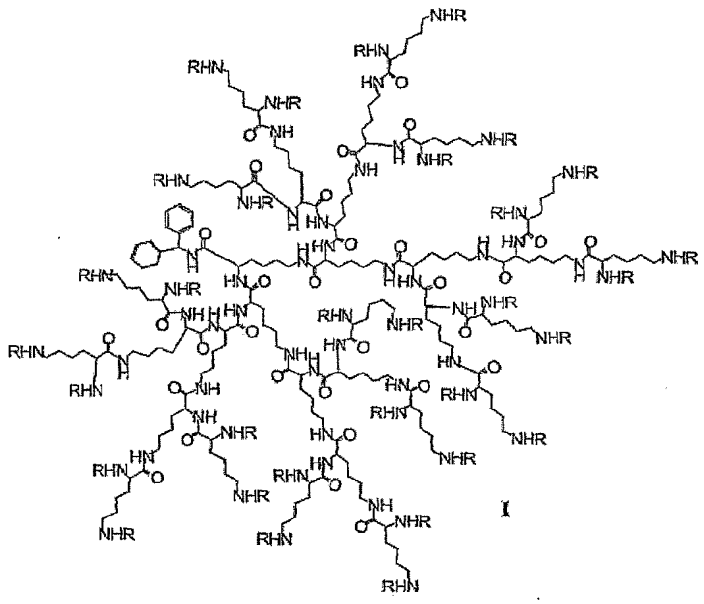
18. A microbicidal delivery system according to claim 1, wherein the microbicidal composition is carried on an external surface of the prophylactic device.

19. A microbicidal delivery system according to claim 1, wherein the microbicidal composition is impregnated into the prophylactic device.

20. A microbicidal delivery system according to claim 1, wherein the microbicidal composition is covalently bound to a surface of the prophylactic device.

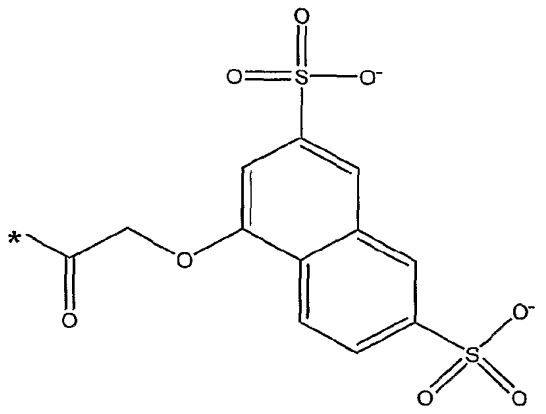
21. A microbicidal delivery system including

a microbicidal compound of formula I



I

where R represents a group of the formula IV



IV;

a carrier, excipient or diluent therefor; and

a condom;

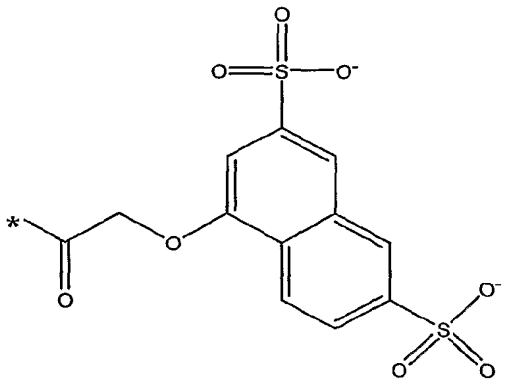
the microbicidal composition being carried on a surface of the condom and being compatible therewith.

22. A microbicidal delivery system according to claim 21, wherein the microbicidal composition is carried on an external surface, and/or an internal surface of the condom.

23. A microbicidal delivery system according to claim 22, wherein the microbicidal composition covers at least a substantial portion of the external surface and/or the internal surface of the condom.

24. A microbicidal composition including

a microbicidal compound including a dendrimer including one or more surface groups of formula IV

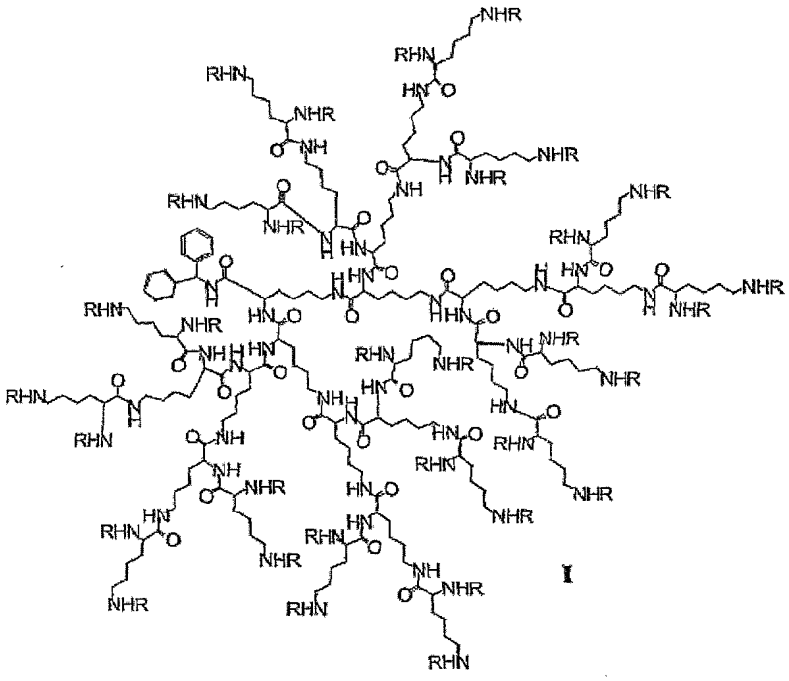


IV

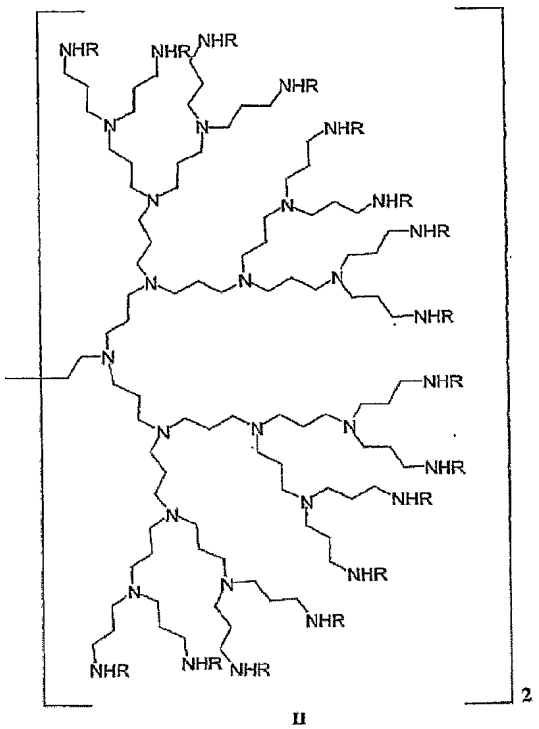
a microbicidally active derivative thereof, or pharmaceutically acceptable salt or solvate thereof; and

a secondary pharmaceutically active composition; and

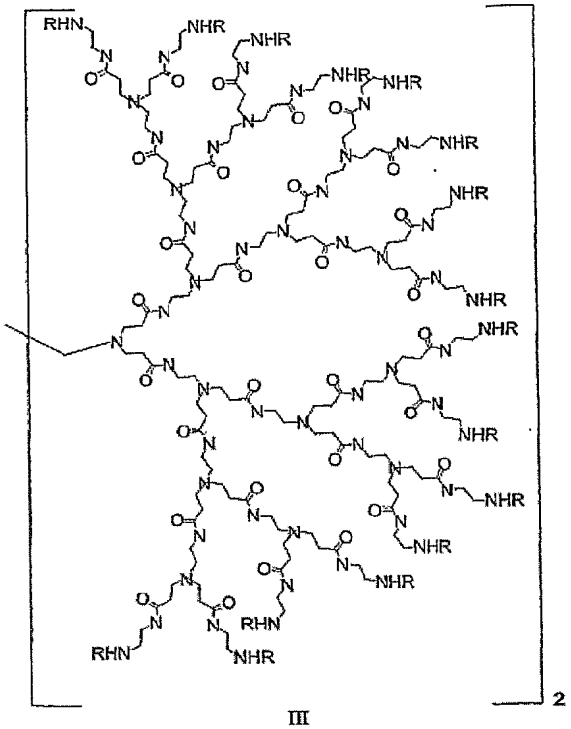
25. A microbicidal composition according to claim 24 wherein the microbicidal compound is selected from one or more of the compounds of formula I, II or III



I

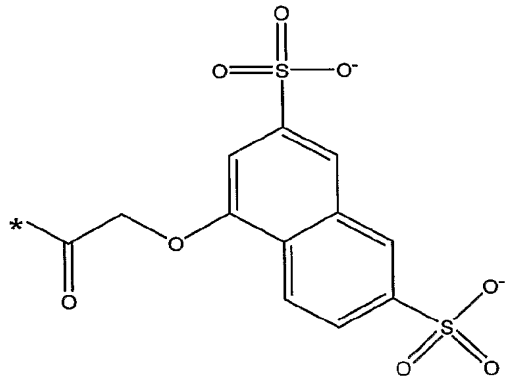


II



III

where R represents a group of the formula IV



IV.

26. A microbicidal composition according to claim 24, wherein the microbicidal compound is present in the microbicidal composition in an amount of from about 0.5% to 20% weight/weight.

27. A microbicidal composition according to claim 26, wherein the microbicidal compound is present in the microbicidal composition in an amount of from about 2% to 15% weight/weight.

28. A microbicidal composition according to claim 24, wherein the microbicidal composition is present in an amount of from about 0.25 to 2 g.

29. A microbicidal composition according to claim 24, wherein the secondary pharmaceutically active compound is a contraceptive or an agent active against sexually transmitted infections.

30. A method for the prevention of sexually transmitted infections in a human patient, including providing a microbicidal delivery system according to claim 1.

31. A method according to claim 30, wherein the disease is a vaginally, rectally or orally transmitted sexually transmitted infection selected from one or more of the group consisting of HSV-1, HSV-2, HIV-1, HIV-2 and HPV infection and *Chlamydia trachomatis* infection.

32 Use of a microbicidal compound according to claim 1, a microbicidally active derivative thereof, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a microbicidal delivery system for the prevention of sexually transmitted infections in a human patient.

33. Use of a compound of formula I, II or III according to claim 2, a microbicidally active derivative thereof, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a microbicidal delivery system for the prevention of sexually transmitted infections in a human patient.

34. Use according to claim 32, wherein the disease is a vaginally, rectally or orally transmitted sexually transmitted infection selected from HSV-1, HSV-2, HIV-1, HIV-2 and HPV infection and *Chlamydia trachomatis* infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/000120

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 31/785 (2006.01) ***A61F 6/08*** (2006.01) ***A61P 31/12*** (2006.01)
A61F 6/04 (2006.01) ***A61F 6/10*** (2006.01) ***A61P 31/18*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI, Medline, CAPlus: dendrimer, starburst, spl7013, viva gel, spl7304, spl7320, polylysine, polyamidoamine, polypropyleneimine, pamam, microbicide, sexual, hiv, hsv, hpv, Chlamydia, c trachomatis, herpes, candida, papilomavirus, prophylactic, condom, cervical cap, diaphragm, vaginal sponge, pessary

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2000/015240A (Starpharma Limited) 23 March 2000 See whole document	1 to 34
X	WO 2000/015239A (Starpharma Limited) 23 March 2000 See whole document	1 to 34
X	WO 2002/079298A (Starpharma Limited) 10 October 2002 See whole document	1 to 34

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2006	- 6 MAR 2006
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **Michael Grieve** Telephone No : (02) 6283 2267

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/000120

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/079299A (Starpharma Limited) 10 October 2002 See whole document	1 to 34
X	WO 1995/034595A (Biomolecular Research Institute Ltd) 21 December 1995 See whole document	1 to 34
A	Bourne, N. et al. "Dendrimers, a New Class of Candidate Topical Microbicides with Activity against Herpes Simplex Virus Infection" Antimicrobial Agents and Chemotherapy Vol.44(9) (2000) pages 2471 to 2474 See whole document	1 to 34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2006/000120

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	0015240	AU	58416/99	BR	9913712	CA	2343113
		CN	1323214	EP	1113806	NZ	510289
		US	6464971	US	2003129158		
WO	0015239	AU	58415/99	BR	9913718	CA	2343205
		CN	1323215	EP	1113805	NZ	510376
WO	02079298						
WO	02079299	BR	0208411	CA	2441357	CN	1503816
		EP	1399499	US	2005008611		
WO	9534595	AU	26659/95	BR	9508031	CA	2192446
		CN	1154123	EP	0765357	NZ	287819
		US	6190650				

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX